

Assessing cross-reactivity in allergen immunotherapy

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ABSTRACT

Knowledge of patterns of pollen cross-reactivity is crucial for formulation of immunotherapy vaccines. As phylogenetic relationships have become better clarified through the use of tools such as gene sequencing, it is apparent that cross-reactivity reflects taxonomy in the vast majority of cases. Contradictory observations of unexpected cross-reactivity between distantly related plants require explanation. There are many proteins, presumably performing vital functions, tightly preserved throughout the evolutionary tree from plants to animals. Examples are profilins, lipid transfer proteins, and pathogenesis-related proteins. These may function as panallergens. The small differences that exist between these ubiquitous proteins may explain why these are frequently minor allergens, not reacting in the majority of allergic sera. This article summarizes cross-reactivity from older studies using crude pollen extracts as well as newer research of purified or recombinant allergenic proteins. The patterns of cross-allergenecity that emerge should be helpful in guiding therapeutic decisions.

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Why should pollen cross-reactivity be of concern in the clinical setting? Allergic travelers could research what flora may be found where they are visiting. Without a sense of whether nonendemic plants are allergenically related to those they are sensitive to, they cannot adequately prepare for possible exposures. A knowledge of allergen cross-reactivity will allow the allergist to better formulate immunotherapy, avoiding the addition of too many similar allergens and thus decreasing the likelihood of systemic reactions to overly potent extracts, and allowing appropriate coverage in formulation. A great deal of information has become available over the past 50 years, both on pollen cross-allergenecity and plant systematics. Advances have been made with amino acid sequencing, gene sequencing, and cloning of recombinant allergens.

Pollen Interrelationships

Cross-reactivity inferred by plant systematics depends on two premises.¹ First, the present botanical classification truly reflects phylogeny, that is, that two plants found in the same genus evolved from a common recent progenitor, two in the same family from a more distant ancestor, and so forth. The second premise is that plants

in the same genus would have the greatest number of shared allergens, those in the same family perhaps less, and distantly related plants would be expected to show little cross-reactivity. This has been generally validated, but there are exceptions, notably, panallergens such as profilins, nonspecific lipid transfer proteins, and pathogenesis-related proteins.^{2,3} The taxonomy used here is that of Judd and colleagues in *Plant Systematics: A Phylogenetic Approach*.⁴ Their supporting data are derived from morphology, embryology, palynology, and analysis of biochemical, chloroplast gene, chromosome, and DNA data. Taxons of any size, including orders or classes, related by a common ancestor are called clades. Where monophyly, descent from a common ancestor, is very likely, one would expect strong cross-reactivity. However, controversy persists in the systematics of numerous plant groups.

Seed plants are split into gymnosperms (conifers) and angiosperms (flowering plants). Monophyly of angiosperms is strongly supported, but that of the gymnosperms is not. The traditional division of flowering plants into Monocotyledoneae and Dicotyledoneae is not supported by recent data: Monocots *are* monophylous, while Dicots are not. A large monophylous subset of Dicots is the Tricolpates. This group is characterized by similar gene sequences and by pollen grains with three apertures (although there are frequent exceptions).

Conifers. The largest family in the order Pinales is Cupressaceae. This group includes cedars, junipers, cypresses and others. Family members have a strongly cross-reactive major allergen.⁵ A number of Cupressaceae allergens have now been cloned. The pine family, Pinaceae, contains pines, spruces, hemlocks, and firs. Crude extracts of Pinaceae members have not shown cross-reactivity with Cupressaceae plants. Members of Pinaceae are rarely potent sensitizers, and may frequently be ignored in formulating extracts.

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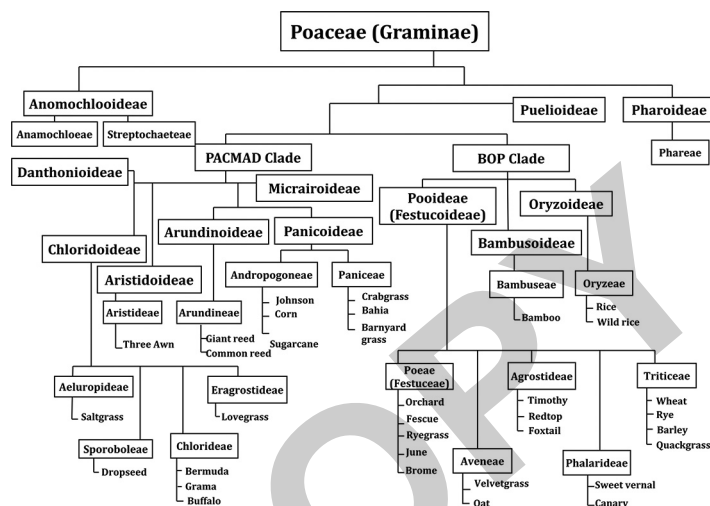


Figure 1. Family Poaceae taxonomy.

Table 1 Grass pollen interrelationships

Taxon	Examples	Comments
Poaceae Pooideae	Timothy, orchard, fescue, ryegrass, june, sweet vernal	1. Strong cross-allergenicity based on marked homology of group 1, 2/3, 5 major allergens 2. Possible unique allergens in timothy and sweet vernal
Poaceae Chloridoideae	Bermuda, buffalo, salt, grama	1. Cross-reactivity between members, Bermuda strongest inhibitor 2. Lack of group 2 and 5 allergens accounts for little cross-allergenicity with Pooideae
Poaceae Panicoideae	Johnson, corn, bahia, sugarcane	1. Lack of group 2 and 5 allergens accounts for little cross-allergenicity with Pooideae 2. More cross-reactivity with Pooideae than Chloridoideae
Juncaceae, Cyperaceae, Typhaceae, Areceae	Rush, sedge, cattail, palm	1. Cross-allergenicity within families 2. No cross-reactivity with Poaceae

Grasses. The Monocot subclass is composed of the lily superorder Liliales, and the spiderwort superorder Commelinales. The family Poaceae is a large clade within the latter superorder, with other families containing rushes, sedges, and cattails. Poaceae has two major clades and three additional minor subfamilies (Fig. 1). There are numerous tribes. The PACMAD clade contains the subfamilies Panicoideae, Arundinoideae, Chloridoideae, Micrairoideae, Aristidoideae, and Danthonioideae, hence the acronymic clade name. The BOP clade consists of the subfamilies Bambusoideae, Oryzoideae, and Pooideae. The subfamily Pooideae (temperate pasture grasses) contains five tribes. Panicoideae contains two tribes, Andropogoneae and Paniceae. Chloridoideae has four tribes: Chlorideae, Aeluropideae, Eragrostideae, and Sporoboleae.

Members of Pooideae are strongly cross-reactive, based on crude extract studies and specific major

allergen studies.⁶ Other subfamilies show less cross-reactivity. Bermuda grass (tribe Chlorideae) does not strongly cross-react with the northern grasses, based on relative lack of major allergen groups 2 and 5. Two other southern grasses, Johnson (tribe Andropogoneae) and Bahia (tribe Paniceae), were inhibited by the temperate grasses, but were in turn poor inhibitors, suggesting they also lacked certain major allergens (Table 1). About 30 individual grass allergens have been described.

Tricolpate Angiosperms. Three clades within tricolpates contain most of the plants incriminated in pollinosis: the subclasses Asteridae and Rosidae, and the superorder Caryophyllales. The latter taxon includes the orders Caryophyllales and Polygonales. Within Caryophyllales, chenopod-amaranth plants are common weeds of the Amaranthaceae family. This weed group contains major inducers of pollinosis in the

Table 2 Tree and weed interrelationships

Taxon	Examples	Comments
Pinales (Coniferales) Cupressaceae	Cedar, juniper, mountain cedar, cypress, Japanese red cedar, redwood, pine	1. Strong cross-allergenicity within Cupressaceae based on marked homology of group 1 and 2 major allergens 2. Weak cross-allergenicity with angiosperms may be because of group 4 calcium binding proteins
Pinales (Coniferales) Pinaceae	Pine, spruce, hemlock, Douglas fir, larch, fir	1. Minimal cross-inhibition between Monterey pine and ryegrass most likely because of profilins 2. No cross-inhibition with Cupressaceae
Caryophyllanae Caryophyllales Amaranthaceae Amaranthioideae	Palmer's amaranth, redroot pigweed, western waterhemp	1. Strong cross-allergenicity between Amaranthus species, especially with Palmer's amaranth and redroot pigweed, somewhat less with western waterhemp
Caryophyllanae Caryophyllales Amaranthaceae Chenopodioideae	Russian thistle, burning bush, annual saltbush, wingscale	1. Strong cross-allergenicity between Atriplex species (scales) 2. Greater diversity, with variable degrees of cross-reactivity with other subfamily Chenopodioideae members 3. Russian thistle may possess unique allergens
Fagales Fagaceae	Beech, oak	1. Fairly strong cross-allergenicity between Betulaceae and Fagaceae members based on homology of group 1 and 2 allergens
Fagales Betulaceae	Birch, alder, hazel	1. Strong cross-allergenicity between Betulaceae members based on homology of group 1 and 2 allergens 2. Fairly strong cross-allergenicity between Betulaceae and Fagaceae members based on homology of group 1 and 2 allergens
Lamiales Oleaceae	Olive, ash, privet, lilac	1. Strong cross-allergenicity between Oleaceae members based on homology of group 1 allergens 2. Group 3 calcium-binding proteins cross-react
Asterales Asteraceae Heliantheae	Ragweed, marshelder, cocklebur	1. Strong cross-allergenicity between short, giant, western, and false ragweed 2. Slender and southern ragweed less potent 3. Minor to little cross-reactivity between ragweed and mugwort, marshelder, or cocklebur
Asterales Asteraceae Anthemideae	Giant sagebrush, mugwort	1. Strong cross-allergenicity between Artemisia species 2. Minor to little cross-reactivity between mugwort and ragweed, marshelder, or cocklebur

western and Great Plains states, including tumbleweeds (*Salsola* and *Kochia*), scales (*Atriplex spp*), and pigweeds (*Amaranthus spp*). Numerous studies show very strong cross-reactivity between *Amaranthus* species, and likewise between *Atriplex* species. Cross-reactivity between other family members is variable (Table 2). The tumbleweed Russian thistle, *Kali tragus* (prior to 2007 known as *Salsola kali* or *S. pestifer*), has seven characterized allergens still identified by the older name, *Sal k* 1–7.

The two subclades of Rosidae (Eurosids I and Eurosids II) have pollinosis-inducing members. The first subclade contains several orders with strongly

allergenic plants: Rosales, Fagales, Fabales, and Malpighiales (Fig. 2). The suborder Urticineae, within Rosales, contains the families Ulmaceae, Moraceae, Urticaceae, and Cannabaceae. Urticaceae contains nettle, *Urtica spp*, and pellitory, *Parietaria spp*; the latter are major aeroallergens in the Mediterranean basin. *Parietaria judaica* and *P. officinalis* are strongly cross-reactive.⁷ The order Malpighiales contains Euphorbiaceae and Salicaceae; the latter family contains cottonwoods, poplars, and aspens (*Populus spp*) and willows (*Salix spp*). Apparent strong cross-reactivity within this family is based on skin test correlations

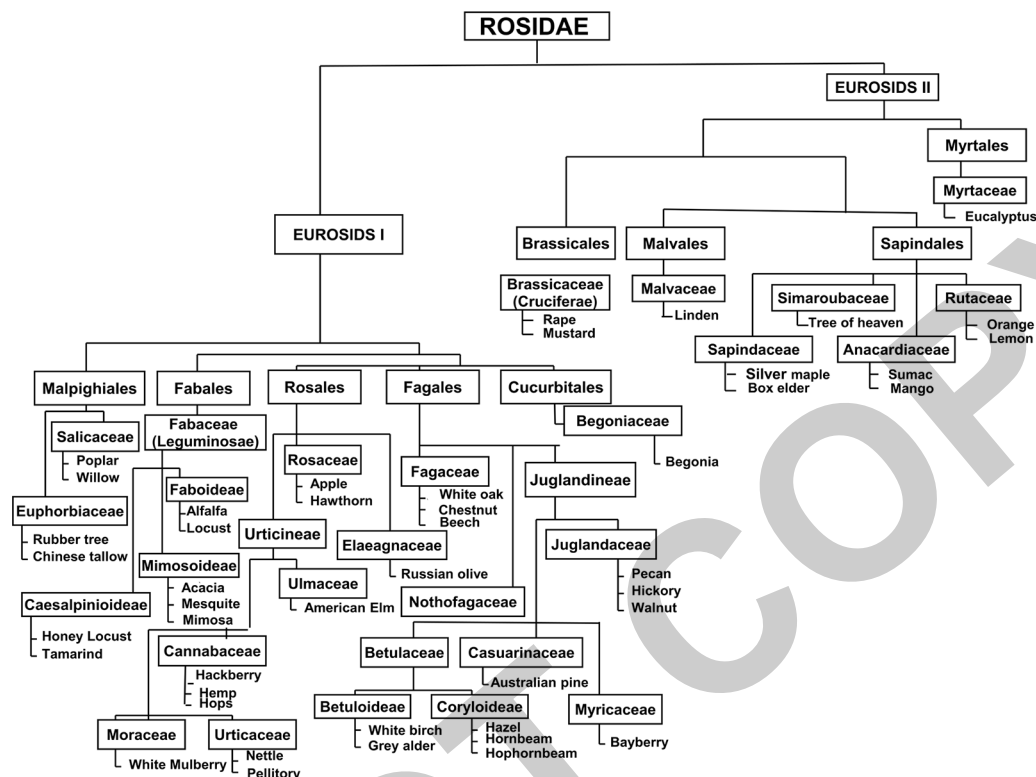


Figure 2. Class Rosidae taxonomy.

and Prausnitz–Küstner neutralization. Moderate cross-reactivity between Salicaceae and Fagales members is defined by older inhibition techniques.

The beech family, Fagaceae, is one branch of the order Fagales, and another large arm is the Juglandineae sub-order, including the birch family, Betulaceae, and the walnut family, Juglandaceae. The latter contains walnut, pecan, and hickory. Shagbark hickory and pecan have strong skin test correlations but less with black walnut. Skin test correlations and radioallergosorbent test (RAST) determinations support the cross-reactivity of the beech and birch families. Multiple studies purifying, characterizing, and sequencing of Betulaceae major allergens have been performed. Recombinant DNA studies showed strong homology between the major allergen of birch, Bet v 1, and the major allergens of other family members.^{8,9} Molecular profiling of allergens has clarified tree interrelationships.¹⁰

The second Rosidae subclade (Eurosids II) accommodates diverse allergenic plants. Oilseed rape (*Brassica napus*) in Brassicaceae is a heavily cultivated turnip-like aeroallergenic plant, with allergens of 6–8 and 14 kDa weights, as well as higher molecular allergens from 27 to 69 kDa. The order Sapindales includes Sapindaceae, Rutaceae, Simaroubaceae, and Anacardiaceae. Maples, *Acer spp*, and boxelder, *Acer negundo*, are in Sapindaceae. Old studies show modest cross-reactivity between maple and Fagales members, but little is found with boxelder. Some botanists

have suggested boxelder should be in a separate genus (Table 2).

The majority of the subclass Asteridae is divided between two groups (Fig. 3). The first group, Euasterids I, contains the orders Lamiales, Garryales, Gentianales, and Solanales. The latter order includes the Australian weed, Paterson's curse. Lamiales contains the olive and plantain families. Oleaceae has shrubs such as lilac and forsythia as well as ash and olive trees. Strong familial cross-reactivity was demonstrated using RAST inhibition, isoelectric focusing, and tandem cross-immuno-electrophoresis, with olive generally being the strongest inhibitor.¹¹ Fifteen olive allergens have been characterized. There are shared high molecular weight allergens between birch and ash.

Asteraceae (Compositae) is a huge family with 3 subfamilies and 17 tribes. The subfamily Asteroideae is monophyletic, and contains 10 tribes, of which 3 are of particular interest to allergists: the sunflower tribe, Heliantheae; the aster tribe, Astereae; and the mayweed tribe, Anthemideae. Ragweeds are in the sunflower tribe. There are numerous species, with four major ragweeds being short, giant, western, and false. Other members of subtribe Ambrosiinae include povertyweed, marshelder, and cocklebur. Anthemideae includes mugwort and other sages, and Astereae contains goldenrod and baccharis. Allergenic identity of short and giant ragweeds was shown by skin test comparisons, Prausnitz–Küstner

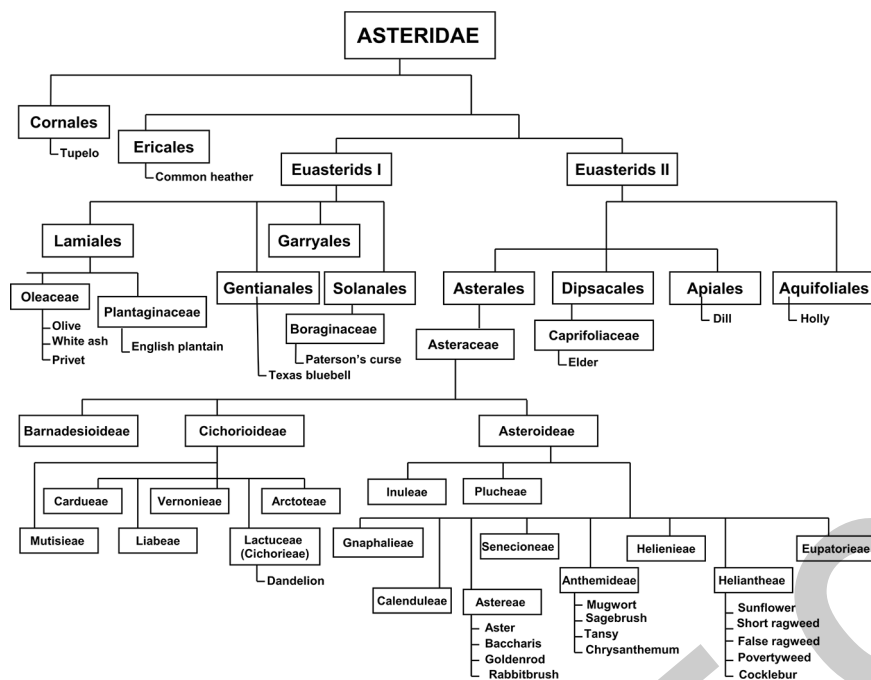


Figure 3. Class Asteridae taxonomy.

neutralization, and immunotherapy extract interchangeability; however others have reported inadequacy of monospecies immunotherapy, skin test disparities, incomplete Prausnitz–Küstner neutralization with whole or partially purified extracts, and nonidentity of precipitins on Ouchterlony immunodiffusion. Comparison of the four major ragweeds by RAST inhibition found them roughly equivalent, with false ragweed being the most effective inhibitor.¹² Leiferman and associates found overlapping RAST inhibition curves for short, giant, western and false ragweeds; slender and southern ragweeds were less potent; and other members of the family showed no inhibition.¹³ Sera from U.S. and Indian patients demonstrated marked cross-inhibition between among ragweed, giant ragweed, and feverfew, *Chrysanthemum parthenium*. Twelve short ragweed allergens have been characterized or cloned, the most important being Amb a 1 (Ag E).

Two studies using enzyme-linked immunosorbent assay inhibition and immunoblot inhibition examined cross-reactivity in 6–9 *Artemisia* species.^{14,15} Inhibition of immunoblots was virtually complete among the nine species. Nine *Artemisia* allergens have been identified, including Art v 1, a 60 kDa glycoprotein; Art v 2, a 35 kDa glycoprotein; and Art v 3, a nonspecific lipid transfer protein; with the former showing cross-reactivity with ragweed, and the second with birch (Table 2).

Fungal Interrelationships

Cross-reactivity data for fungi had been confused because of the older classification system using

artificial form genera. The Class Deuteromycetes, or Fungi Imperfecti, comprised members with distinct morphology, but many of these represented only the asexual life forms of fungal organisms. More recently, DNA sequencing has allowed a better phylogenetic classification, so the former taxonomy is no longer valid.¹⁶

More than two dozen allergens of *Aspergillus fumigatus* have been characterized.¹⁷ A major allergen of *A. fumigatus*, Asp f 1, has 95% sequence homology with mitogillin, an 18 kDa cytotoxin from *A. restrictus*.¹⁸ A monoclonal antibody against the 68 kDa *Penicillium notatum* major allergen (Pen n 20) reacts with *Aspergillus flavus*, *A. terreus*, *A. fumigatus*, *A. niger*, and two other *Penicillium* species. Anti-*Penicillium* species and anti-*Aspergillus* species monoclonal antibodies did not show any cross-reactivity with *Alternaria*, *Aureobasidium*, *Cladosporium*, *Curvularia*, *Stachybotrys*, or *Ulocladium*. Several species of *Penicillium* have an alkaline serine proteinase allergen with homology to the vacuolar serine proteinase from *A. fumigatus*.¹⁸

Varying degrees of cross-reactivity have been shown among *Alternaria*, *Stemphylium*, *Curvularia*, and *Stachybotrys*. RAST inhibition and immunoblot studies have shown little to no inhibition among *Aspergillus fumigatus* and *Alternaria tenuis* and *Cladosporium herbarum*, whereas the latter two showed considerable cross-reactivity with similar slopes on inhibition curves. The major *Alternaria* antigen, Alt a 1, is as abundant in *Stemphylium* as in *Alternaria*.¹⁹ *Cladosporium*, and *Alternaria* have homologous allergens.²⁰ About 50% of *Cladosporium*- and *Alternaria*-sensitive patients react to recombinant enolases,

and inhibition studies showed essential identity between the two.

Cross-reactivity of yeasts has been investigated using skin test correlations and rabbit antisera enzyme immunoassay inhibition. Although there was marked skin test concordance among *Candida* species, *Rhodotorula*, *Saccharomyces*, and others, significant immunoassay cross-reactivity was only seen between the *Candida* species. Cross-reactivity between *Candida albicans* and baker's yeast, *Saccharomyces cerevisiae*, is largely due to enolase. Cross-reactivity has been shown between *C. albicans* and *Pityrosporum orbiculare*.¹⁸

Basidiomycetes include large fungi such as mushrooms and bracket fungi as well as smuts and rusts. They have been implicated in seasonal allergy as well as epidemic asthma. Allergenicity of the bracket fungi *Ganoderma applanatum* has been investigated, and no cross-reactivity with rabbit antisera to other common molds such as *Alternaria*, *Aspergillus*, *Candida*, *Penicillium*, *Epicoecum*, or *Helminthosporium* was found. Three members of the Basidiomycete order Agaricales (*Coprinus quadrifidus*, *Psilocybe cubensis*, and *Pleurotus ostreatus*) as well as *Calvatia cyathiformis* (order Lycoperdales) show strong cross-reactivity, with little to no inhibition demonstrated with *Ganoderma meredithae* (Aphylophorales) or *Pisolithus tinctorius* (Sclerodermatales).

Summary

Taxonomy remains the major guide in assessing the likelihood of cross-reactivity between aeroallergens and is accurate in the great majority of cases. Refinement of plant systematics with clarification of phylogenetic relationships has demonstrated that this basic premise holds true. Unexpected cross-allergenicity between distantly related plants is usually because of sensitization to pan-allergens, ubiquitous tightly preserved proteins, and even across plants and animals such as profilins, nonspecific lipid transfer proteins, and pathogenesis-related proteins). The small differences that exist between these ubiquitous proteins explains why these are frequently only minor allergens.

Conifers. Cupressaceae members are markedly cross-reactive. A single *Juniperus* pollen extract should be suitable for immunotherapy. Members of Pinaceae should be treated separately in the rare instance of clinical importance. There is no significant cross-reactivity between conifers and flowering plants; the minor reactivity is not of clinical relevance.

Grasses and Related Plants. Members of the grass subfamily Pooideae are strongly cross-reactive based on marked homology of groups 1, 2/3, 4, and 5, most of which are major allergens. Differences in cross-inhibition probably reflect quantitative differences rather

than qualitative ones, although it is possible that timothy and sweet vernal may contain relevant unique allergens. In testing with, and immunotherapy for, northern pasture grasses, adequate coverage should be achieved by one or two members, and there is no need for multiple representation. The Panicoideae and Chloridoideae subfamilies show greater diversity and lack group 2 and group 5 allergens, accounting for their differences with the temperate grasses. Members should be tested and treated separately. Chloridoideae members appear to be cross-reactive, with Bermuda grass being very potent, and are the appropriate choice to cover other members. The cross-reacting profilins and calcium-binding allergens are minor allergens. Other nongrass families of monocots show reactivity between members but no appreciable cross-reactivity with grasses.

Tricolpate Angiosperms. Diversity is the rule among the plants of these subclasses and orders. Lack of cross-reactivity is the rule even down sometimes to the level of tribe. There are, however, exceptions, with significant cross-reactivity across certain families.

In Amaranthaceae, allergenic identity is almost complete among the *Amaranthus* species such as redroot pigweed and Palmer's amaranth, and slightly less with another member, western water-hemp. In the Chenopodioideae, there is greater diversity, although there are striking similarities among the *Atriplex* saltbushes and scales. There are varying degrees of cross-inhibition between other chenopods and amaranths, and Russian thistle appears to possess significant unique allergens. *Amaranthus* and *Atriplex* species can be represented by single members, but the other locally relevant members need to be addressed separately.

The order Fagales shows strong cross-allergenicity within the birch family extending across to the beech family as well. Use of the locally prevalent Betulaceae member should cover other family members as well. In areas where oaks are predominant, a *Quercus* would be expected to cover birch as well. Immunotherapy with rBet v 1 and rBet v 2 recombinant allergens could effectively cover Fagales tree pollen sensitivity. There is scant information concerning other members of the Rosidae subclass. Generally, one member of a family can be expected to be adequate for immunotherapy, although there are exceptions such as nettle and pellitory.

Olive family members are strongly cross-reactive. In areas where European olive is grown, it seems the proper choice. In other areas where ash is prevalent, it should be adequate. Treating with multiple members should not be necessary.

Asteraceae members show variable cross-reactivity. The four major ragweeds (short, giant, western, and

false) strongly cross-react, and one or two are quite adequate. However, in areas where the sages or marsh-elders are common, these need to be handled separately. Because *Artemisia* species are so strongly cross-reactive, it is not necessary to skin test or treat with multiple members, a single choice will do. In the Midwest and West common sagebrush (*A. tridentata*) seems reasonable, while in the eastern states and Europe, mugwort (*A. vulgaris*) seems most appropriate.

CLINICAL PEARLS

- A knowledge of allergen cross-reactivity will allow the allergist to better formulate immunotherapy, avoiding the addition of too many similar allergens and thus decreasing the likelihood of systemic reactions to overly potent extracts, and allowing appropriate coverage in formulation.
- Temperate pasture grasses (Pooideae) are strongly cross-reactive and therefore may be represented by a single member in allergen immunotherapy formulations. Timothy appears more potent than other Pooideae, and crude extract studies suggest it may have a unique allergen and therefore may be the best choice of Pooideae in extract formulation.
- Within family cross-reactivity is strong for the cypress, birch, beech, and olive tree families, as well as across family boundaries with birch and beech. Therefore, single members should be adequate to represent these families in allergen extracts.
- Although maple and boxelder are classified in the same genus, *Acer*, older research demonstrates that there are distinct differences in cross-inhibition with other plants. Some botanists believe boxelder should be reclassified in a separate genus. Therefore, they should be treated as different entities.
- The major *Amaranthus* weeds, Palmer's amaranth and redroot pigweed, are essentially allergenically identical. Likewise, the *Atriplex* weeds are strongly cross-reactive. For each, use the locally prevalent weed for allergen immunotherapy. Other members of *Amaranthaceae*, such as Russian thistle and burning bush, are less cross-reactive and need to be treated separately.
- The four major ragweeds (short, giant, western, and false) are strongly cross-reactive, so although it is common usage to treat with both short and giant ragweed together, this should not be necessary. Other members of the same tribe, such as povertyweed and cocklebur are not significantly cross-reactive and need to be treated separately.
- *Artemisia* species are strongly cross-reactive. Testing and treating with one species is adequate; suggest use of giant sagebrush, *A. tridentata*, in the western

and central United States and mugwort, *A. vulgaris*, in the eastern United States and Europe.

- Although there is evidence of some cross-reactivity between *Alternaria* and *Cladosporium*, and between *Penicillium* and *Aspergillus*, at the present it is probably prudent to treat these separately.

REFERENCES

1. Weber RW. Cross-reactivity of plant and animal allergens. *Clin Rev Allergy Immunol*. 2001; 21:153.
2. Kleine-Tebbe J, Ackermann-Simon J, Hanf G. Molecular allergy diagnosis using pollen marker allergens and pollen panallergens: Five patterns seen in multiple test reactions to pollen extracts. *Allergol Select*. 2021; 5:180.
3. Skypala IJ, Asero R, Barber D, Cecchi L, Diaz Perales A, Hoffmann-Sommergruber K, et al. Non-specific lipid-transfer proteins: Allergen structure and function, cross-reactivity, sensitization, and epidemiology. *Clin Transl Allergy*. 2021; 11:e12010.
4. Judd WS, Campbell CS, Kellogg EA, et al. *Plant systematics: A phylogenetic approach*. Sunderland, MA: Sinauer Associates, 1999.
5. Schwiertz LA, Goetz DW, Whisman BA, Reid MJ, et al. Cross-reactivity among conifer pollens. *Ann Allergy Asthma Immunol*. 2000; 84:87.
6. Andersson K, Lidholm J. Characteristics and immunobiology of grass pollen allergens. *Int Arch Allergy Immunol*. 2003; 130:87.
7. Cancelliere N, Iglesias I, Ayuga Á, Enrique Miranda E. Cross-reactivity between *Parietaria judaica* and *Parietaria officinalis* in immunotherapy extracts for the treatment of allergy to *Parietaria*. *Biomed Rep*. 2020; 12:326.
8. Valenta R, Breiteneder H, Pettenburger K, Rumpold H, Kraft D, Scheiner O, et al. Homology of the major birch-pollen allergen, Bet v I, with the major pollen allergens of alder, hazel, and hornbeam at the nucleic acid level as determined by cross-hybridization. *J Allergy Clin Immunol*. 1991; 87:677.
9. Biedermann T, Winther L, Till SJ, Panzner P, Knulst A, Valovirta E. Birch pollen allergy in Europe. *Allergy*. 2019; 74:1237.
10. Asam C, Hofer H, Wolf M, Aglas L, Wallner M. Tree pollen allergens—an update from a molecular perspective. *Allergy*. 2015; 70:1201.
11. Bousquet J, Guérin B, Hewitt B, Lim S, Michel FB. Allergy in the Mediterranean area. III: Cross reactivity among Oleaceae pollens. *Clin Allergy*. 1985; 15:439.
12. Bernstein IL, Perera M, Gallagher J, Michael JG, Johansson SG. In vitro cross-allergenicity of major aeroallergenic pollens by the radioallergosorbent technique. *J Allergy Clin Immunol*. 1976; 57:141.
13. Leiferman KM, Gleich GJ, Jones RT. Cross-reactivity of IgE antibodies with pollen allergens. II. Analyses of various species of ragweed and other fall weed pollens. *J Allergy Clin Immunol*. 1976; 58:140.
14. Hirschwehr R, Heppner C, Spitzauer S, Sperr WR, Valent P, Berger U, et al. Identification of common allergenic structures in mugwort and ragweed pollen. *J Allergy Clin Immunol*. 1998; 101:196.
15. Katial RK, Lin FL, Stafford WW, Ledoux RA, Westley CR, Weber RW. Mugwort and sage (*Artemisia*) pollen cross-reactivity: ELISA inhibition and immunoblot evaluation. *Ann Allergy Asthma Immunol*. 1997; 79:340.
16. Hobbitt DS, Blackwell M, James TY, Spatafora JW, Taylor JW, Vilgalys R. Phylogenetic taxon definitions for Fungi, Dikarya, Ascomycota and Basidiomycota. *IMA FUNGUS*. 2018; 9:291.

17. WHO/IUIS Allergen Nomenclature Sub-Committee. Allergen nomenclature. Available online at allergen.org; accessed November 30, 2021.
18. Fukutomi Y, Taniguchi M. Sensitization to fungal allergens: resolved and unresolved issues. *Allergol Int.* 2015; 64:321.
19. Sáenz-de-Santamaría M, Postigo I, Gutiérrez-Rodríguez A, Cardona G, Guisantes JA, Asturias J, et al. The major allergen of *Alternaria alternata* (alt a 1) is expressed in other members of the Pleosporaceae family. *Mycoses.* 2006; 49:91.
20. Twaroch TE, Curin M, Sterflinger K, Focke-Tejkl M, Swoboda I, Valenta R. Specific antibodies for the detection of *Alternaria* allergens and the identification of cross-reactive antigens of other fungi. *Int Arch Allergy Immunol.* 2016; 170:269. □